the 15th century French folk saying which guided Dr Edward Livingston Trudeau in his care of patients with tuberculosis a century ago:

To cure sometimes,
To relieve often,
To comfort always.

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Some Gods Have Feet of Clay

DURING the last few months some of the gods of modern science and technology have seemed more and more to have feet of clay. Certainly there have been, and still are, many who are worshiping these gods and all the blessings that high technology has wrought. Nonetheless, the recent series of tragic, embarrassing and costly failures in the space program of the United States and the frightening explosion of a nuclear reactor in the Soviet Union, with its almost worldwide fallout, have been very sobering events. It has been clearly demonstrated that even the best technology is only relatively dependable, and that human factors must always enter the equation, whether in exercising or not exercising human judgment, or in the human fallout when there is an unexpected technologic failure or disaster.

Perhaps these truly sobering events will focus attention once again on the humanity that pervades this world of increasingly useful yet often risky technology. We are living at a time when worship of science and technology—whether in medicine, in the production of energy, in space or wherever—has been almost pervasive throughout our society. High tech is not supposed to fail, and when it does it is held that "something went wrong," and too often there has been a tragedy.

It may not be too soon for humanity to come to more realistic terms with modern science and high technology. The issue has already come to a head in medicine, where it is being discovered that medical science and technology are not and never will be unerringly effective. Society has yet to come to grips with this reality. The fact is that in medicine there are always probabilities of success and of failure, and there is always the possibility of human error. The same holds true for nuclear reactors and the launching and operation of space vehicles. Quite evidently, this has to be true of all modern science and technology, wherever it is.

Risk is inherent in health care and in all aspects of human life. To the extent humans are free and aware, they can assess their personal risks and act accordingly. The human hope and even expectation have been that science and technology can be made risk free. But this can never be. Science and technology, and even physicians, are all useful and even necessary, but none can be infallible. A blind and unthinking faith in human and technologic perfection (which does not exist and is simply unattainable) should be replaced by thoughtful weighing of the probabilities for success or failure and, if there is failure, the likely fallout of whatever kind.

Perhaps we should now begin to ask whether, in the long run, nuclear power and war in space will be worth their risk to humanity, especially since these particular gods have now so clearly shown their feet of clay.

MSMW

Digitalis—A Bicentennial Progress Report

IN THIS ISSUE of the journal, Bhatia has nicely summarized the current status of the clinical entity of digitalis toxicity. At least four developments over the past 15 years have reduced substantially the incidence of this important clinical problem. The first of these is an improved understanding of digoxin pharmacokinetics by clinicians—in particular, an enhanced awareness of the importance of renal excretion as a determinant of the appropriate daily maintenance digoxin dose. Second, serum digoxin concentration measurements are now widely available in clinical laboratories. While overutilized at times, such data are useful in the assessment of unexpected responses to digoxin therapy. Third, the bioavailability of digoxin in preparations for oral use is now far more uniform since the introduction of explicit standards by the Food and Drug Administration (FDA) and the United States Pharmacopeial Convention. And, fourth, improvements in the therapeutic armamentarium for management of congestive heart failure (such as loop diuretics and vasodilators) and supraventricular tachyarrhythmias (such as β-adrenergic blocking agents and the calcium channel blockers verapamil and diltiazem) now render largely obsolete the practice of "pushing" digitalis glycoside doses to maximal tolerated levels. Regarding this last point, there is no solid evidence from clinical studies to indicate that further inotropic benefit is realized by pushing serum concentrations of digoxin above the 1.5 to 2.0 ng per ml range, whereas there is no doubt that the incidence of overtly toxic rhythm disturbances increases substantially as levels higher than this are reached.

Lindenbaum and his colleagues in New York have discovered that about 30% of patients on maintenance digoxin therapy harbor in their lower gastrointestinal tract the saprophytic bacterium *Eubacterium lentum,* which has the enzymatic capacity to convert digoxin to the cardioinactive metabolite dihydrodigoxin and thus to hasten the effective clearance of digoxin. This is quantitatively of clinical importance in at least 10% of patients on a digoxin regimen, who are at risk of a potentially significant increase in their serum

and total body digoxin stores if they receive any of a wide range of antibiotics that rid the gut of *E lentum.*[1]

While all of the above advances in our sophistication regarding the clinical pharmacology of digoxin render the drug safer to use, the fact that 4 million patients in the United States are receiving maintenance digoxin, together with the notoriously narrow margin between therapeutic and toxic doses, ensures that clinically important digitalis toxicity will remain a common problem for the foreseeable future—especially in patients with advanced heart disease in whom it is particularly difficult to distinguish among rhythm disturbances due to digitalis excess, to underlying heart disease or to a combination of both.

Among the noteworthy achievements of the past decade is a much improved understanding of the actions of digitalis glycosides at the cellular level. It has been known for about 25 years that cardiac glycosides inhibit with high affinity and specificity the sodium pump of intact cells; the binding site or "receptor" is now known to reside at an extracellularly facing locus on the α-subunit of sodium-potassium-adenosine triphosphatase, a protein that has now been cloned and sequenced.[2] Occupancy of the receptor blocks the normal outward transport of three Na^+ ions in exchange for the inward transport of two K^+ ions, a process that uses the free energy from cleavage of the terminal high-energy phosphate of adenosine triphosphate to drive these ions uphill against their concentration gradients. In therapeutic (subtoxic) doses, enough pump sites are blocked to produce a modest increase in intracellular Na^+ activity. Through the phenomenon of Na^+-Ca^{++} exchange, this augments intracellular Ca^{++} content and thus enhances contractile force of both normal and failing heart muscle. These same phenomena—sodium-potassium pump blockade and increased intracellular calcium stores—occur to a quantitatively greater degree in the presence of digitalis excess, and underlie the toxic rhythm disturbances that Bhatia has summarized. At still higher and more toxic doses, hyperkalemia can occur (usually in suicidal or accidental overdoses) with ominous prognostic significance.

Bhatia's discussion of the use of purified digoxin-specific Fab fragments in the management of advanced, life-threatening digitalis toxicity is timely in view of the recent approval by the FDA of the release of this new therapeutic modality (generically termed digoxin immune Fab [ovine], or Digibind by Burroughs Wellcome Co.). It is now ten years since we treated the first patient with digoxin-specific Fab fragments derived from sheep polyclonal antibodies,[3] and the subsequent experience in more than 150 patients so treated continues to be gratifying.[4] One cannot resist noting on the frontispiece of William Withering's "Account of the Foxglove and Some of Its Medical Uses," published in 1785, his use of the following quotation from the Ars Poetica of Horace: ". . . *nonumque prematur in annum,*" freely translated "let it be held back until the ninth year." This admonition of Horace to poets not to hasten to press with their work now appears equally apropos of Withering's cautious reporting of his new medicine for treatment of dropsy and of the protracted nature of the development and regulatory agency approval of current therapeutic advances.

For the present, we foresee that the use of digoxin-specific Fab fragments from the polyclonal sheep source will be reserved for potentially life-threatening situations that are (or seem likely to be) resistant to conventional therapeutic modalities. It is appealing to consider the use of similar immunologic approaches to diagnostic as well as therapeutic problems—that is, to use a suitable Fab (or smaller) binding fragment in a sort of "reverse acetyl strophanthidin tolerance test" in which the assured diagnosis that a given rhythm disturbance is due to digitalis intoxication would accompany the abolishment of the arrhythmia. This would be best accomplished using a molecule with appropriate affinity and specificity for cardiac glycosides, but with human immune specificity and hence no risk of development or expression of hypersensitivity. Detailed sequence information on monoclonal antidigoxin antibodies is already available[5] and could in principle be coupled with recombinant DNA technology to yield chimeric antibodies or antibody fragments with selected variable regions joined to different isotypic constant regions.[6]

For the future, there is ample room for improvement in the clinical use of digitalis glycosides. Issues as fundamental as the proper indications for the use of digoxin remain controversial, although a strong consensus now exists that the drug should be used in cases of heart failure for the subset of patients with dilated ventricles that contract poorly, and not in patients with normal-sized left ventricles that contract well but are "stiff" or noncompliant, thus producing dyspnea from elevated filling pressures. Patients with coronary heart disease as well as left ventricular hypertrophy from a variety of causes commonly fit into this latter category and, in general, should not be treated with cardiac glycosides unless supraventricular rhythm disturbances provide an appropriate rationale.

Further refinement of therapeutic indications should be based on randomized trials with stratification for such important variables as age and type and severity of heart disease. In particular, the *incremental* risks and benefits of cardiac glycoside therapy over and above other available modalities including diuretics and vasodilators deserve attention.

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